THE SELECTIVE POSITIVE INOTROPIC ACTIVITY OF 2-ALKYL-1,3-DIOXO-5,10-DIHYDROIMIDAZO[1,5-b]ISOQUINOLINES

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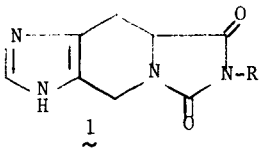
Inotropic selectivity has previously been observed in some 7-alkyl-6,8-dioxo-4,5,9,9a-tetrahydro-1H-diimidazo[3,4-a:4,5-d]pyridines (1, R = H, n-Pr, and C_6H_5) (Steinreich, 1975). In guinea-pig isolated atria 1, R = C_6H_5 at 100 µg/ml caused a 75% increase in force and a slight decrease in rate. The title compounds (Table 1) were synthesised to determine whether the imidazole ring was essential for positive inotropic activity or could be replaced by the aromatic moiety of 2.



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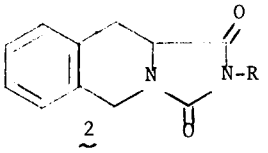

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Table 1. Cardiotonic effects of dihydroimidazo [1,5-b]isoquinolines in guinea-pig isolated atria.

No.	R in 2	Increase Tension* EC50 (µg/ml)	Increase Tension* % of maximum to (-)-isoprenaline	Rate ** Decrease as % of resting rate
3	H	NSE	-	NSE
4	Me	NT	-	NT
5	Et	85	87	NDR to 100 µg/ml (< 10%)
6	n-Pr	54	109	NDR to 100 µg/ml (< 10%)
7	n-Bu	16	11	NSE up to 100 µg/ml
8	Ph	NT	-	NT
9	cyclo-C_6H_{11}	13	3	NSE up to 100 µg/ml

Stock solns 10 mg/ml in DMSO; final organ bath conc.3% DMSO (≡300µg/ml agonist)
*DMSO positive inotropic effects not apparent below 300 µg/ml agonist.
**DMSO negative chronotropic effect not apparent below 100 µg/ml agonist.
NSE = no significant effect. NT = not tested. NDR = non dose-related.

The positive inotropic effects of compounds 5 and 6 were unaffected by propranolol (10^{-7}M), cocaine (1.6×10^{-5}M), mepyramine (1.75×10^{-5}M), burimamide (9×10^{-5}M) and theophylline (2.5×10^{-4}M) and thus the compounds do not appear to exert their actions through β-adrenoceptors either directly or indirectly, nor by the release of histamine or by an action on histamine receptors themselves. The lack of effect of the phosphodiesterase inhibitor theophylline suggests the effect is not mediated via cyclic-AMP.

Steinreich, P. (1975). Ph.D. Thesis, University of Strathclyde.